Cushing's syndrome caused by adrenocortical oncocytoma: A case report

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Received October 11, 2023; Accepted February 8, 2024

DOI: 10.3892/ol.2024.14310

Abstract. Adrenal cortical eosinophilic adenoma usually presents as non-functional adrenal tumor but may lead to Cushing's syndrome in patients. The present article reports a patient with Cushing's syndrome caused by right adrenocortical oncocytoma. The patient was treated in Urology Department of Wuchuan People's Hospital (Zunyi, China) in November 2022 because of hirsutism, weight gain and hypertension. A laparoscopic right adrenal tumor resection was performed using an abdominal approach. Following surgery, blood pressure and heart rate of the patient fluctuated within a healthy range and menstruation returned to normal. Laparoscopic adrenalectomy has obvious advantages over open adrenalectomy, such as less trauma, shorter recovery time and fewer complications. Thus, this treatment for this rare disease is safe and feasible.

Introduction

Eosinophilic adenomas are composed of eosinophils, which are present in numerous parts of the body, including the kidney, salivary, thyroid and pituitary gland, eyelid, thymus and spinal cord. Adrenal cortical eosinophilic adenoma is a rare adrenal tumor. Eosinophilic adenoma of adrenal cortex is often described as nonfunctional adrenal tumor, which may lead to Cushing's syndrome. Adrenal cortical eosinophilic adenoma is a rare pathological type of adrenal tumor (1). Studies have shown that the disease is most common in the left adrenal gland, with a ratio of 2: 1 in the left and 2: 1 in the right, and most common in female patients, with a ratio of 2: 1 in the female:male, with an average onset age of 44 years (1,2). The first adrenocortical oncocytoma was reported by Kakimoto *et al* in 1986 (3). To date, ~200 cases have been reported (4). Adrenal cortical oncocytoma is usually described as non-functional adrenal tumor and may lead to the development of Cushing's syndrome and complex clinical diagnosis. In recent years, with the progress of hospital pathological detection technology, the reporting of this rare disease is on the rise due to the decrease in missed detection and false detection rate (4,5).

Case report

A 30-year-old female patient was admitted to Wuchuan People's Hospital (Zunyi, China) in November 2022 due to increased body hair, weight gain and elevated blood pressure for >1 year. The blood pressure of the patient fluctuated between 150-190 systolic and 80-110 mmHg diastolic. A physical examination revealed a sanguine appearance, centripetal obesity, hypertrophy of the neck and back, small purple lines on the abdomen and armpits and a reduced temperature (35.8˚C) at the ends of limbs. Potassium (4.99 mmol/l; normal reference value, 3.50-5.50 mmol/l), parathormone (35.00 pg/ml; normal reference value, 15.00-65.00 pg/ml), serum creatinine (70.10 μmol/l; normal reference value, 44.00-115.00 μmol/l) and blood calcium (2.42 mmol/l; normal reference value, 2.10-3.00 mmol/l) levels were all within healthy range. In addition, hemoglobin levels were 155 g/l, hematocrit (HCT) was 46.7% and Blood dopamine 67.3 pmol/l (normal value ≤195.7 pmpl/l), blood epinephrine 95.3 pmol/l (normal value ≤605.4 pmpl/l) and blood norepinephrine 590.3 pmol/l (normal value ≤414.0-4,435.5 pmpl/l); 24-h urine dopamine 1,108.28 nmol/24 h (normal value 750.00-2,088.00 nmol/24 h), 24-h urine adrenaline 20.00 nmol/24 h (normal value 4.31-61.60 nmol/24 h), and 24-h urine norepinephrine 147.75 nmol/24 h (normal value 60.00-30). The levels of sex hormones were assessed; results revealed high testosterone levels (7.480 nmol/l, normal value 0.290-1.670 nmol/l) and cortisol levels of 450.10 nmol/l (normal value 63.40-129.60 nmol/l), 473.80 nmol/l (normal value 133.00-537.50 nmol/l) and 533.90 nmol/l (normal value 68.20-327.60 nmol/l) at 12:00 a.m., 8:00 a.m. and 4:00 p.m., respectively. A computed tomography (CT, Philips CT, row 64) scan of the adrenal gland revealed a space (45x40 mm) in the right adrenal gland, indicative of pheochromocytoma or lymphoma (Figs. 1 and 2). Furthermore, there were no abnormalities in renal (Fig. 3) and cervical (Fig. 4) vascular,

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Key words: adrenocortical, oncocytoma, tumor, Cushing's syndrome

gynecological (Fig. 5) and cardiac color Doppler ultrasound (Fig. 6) or CT scan of the skull (Fig. 7). In the present hospital, bone mineral density screening is not a routine preoperative preparation item for patients with adrenal tumors, so the patient was not screened for bone mineral density Following discussions with the department and an additional multidisciplinary team, the following diagnoses were considered for the right adrenal functional tumor: i) Cortical adenoma; ii) pheochromocytoma; iii) cortical cancer; iv) Cushing's syndrome and v) secondary hypertension.

According to the advice of a doctor in the outpatient department of Guizhou Provincial People's Hospital (Guiyang, China), the patient received oral terazosin (2 mg daily, which was gradually adjusted to 2 mg, three times/day) and metoprolol (23.75 mg, once/day) for 2 weeks. Notably, the blood pressure of the patient was uncontrolled; thus, the cardiovascular department was consulted and nifedipine gastrointestinal therapeutic system (20 mg, twice/day) was administered for control. Based on potential pheochromocytoma, preoperative volume expansion preparation was performed. Following adequate blood pressure control and the observation of indexes that reached the standard levels (blood pressure ~120/80 mmHg, heart rate is less than 90 beats/min, and HCT <45%), laparoscopic right adrenal tumor resection was performed under general anesthesia using an abdominal approach. Surgery was performed according to the routine protocols used in the treatment of adrenal tumors (1). Following anesthesia, 100 mg hydrocortisone was administered intravenously and after the completion of surgery, 100 mg hydrocortisone in 5% glucose solution was continuously administered intravenously. During surgery, the highest blood pressure measured was 179/115 mmHg. Following surgery, the blood pressure was 128/90 mmHg. No blood transfusion was performed during the operation.

The tumor of the adrenal gland was 35x60x60 mm^3 in size (Fig. 8), dark brown in color, solid and soft. The inside of the tumor remained dark brown. Pathological examination was performed as follows: Specimen tissues were fixed in 4% paraformaldehyde for 24 h. Dehydration with gradient ethanol and xylene washes. Slice the trimmed wax block on a paraffin slicer with a thickness of 4 μm. Tissue was stained with Harris hematoxylin solution for 5min and eosin solution (95% ethanol solution) for 20 sec. Use Lycra DM2500 microscope for microscopic examination and image collection and analysis. Paraffin-embedded tissue sections showed that the tumor was mainly composed of diffuse eosinophilic epithelial cells. Only acinar, tubular or fascicular structures were observed in the focus area. The postoperative pathology was indicative of adrenocortical eosinophilic adenoma (Fig. 9A and B). The clinical manifestations were hair growth, weight gain, disordered menstrual cycle, fluctuations in blood pressure, centripetal obesity, neck and back hypertrophy, purple lines on the abdomen and armpits and cortisol rhythm disorder. Thus, the patient was diagnosed with Cushing's syndrome caused by adrenocortical oncocytoma. On day 1 following surgery, cortisol levels of 25.04, 28.15 and 31.85 nmol/l were measured at 12:00 a.m., 8:00 a.m. and 4:00 p.m., respectively. The patient exhibited no signs of adrenal failure and both blood pressure and heart rate were in normal ranges at rest. The patient was administered hormone replacement therapy for 1 month, which was gradually reduced. The post-surgery hormone replacement therapeutic regimen was as follows: 200 mg hydrocortisone administered intravenously on day 1; 100 mg hydrocortisone administered intravenously on day 2 and 50 mg hydrocortisone administered orally once/8 h on day 9. On days 10-16, 50 mg hydrocortisone was administered orally once/12 h. On days 17-23, 30 mg hydrocortisone was administered orally every 12 h. On day 24, the dosage was changed to 20 mg and hydrocortisone was administered orally once/12 h. The dosage was gradually reduced to 5 mg/day until day 31. Subsequently, blood pressure and heart rate of the patient fluctuated within healthy range (blood pressure <130/80 mmHg, heart rate <90 beats/min.), and the levels returned to those observed pre-disease. At 3 months post-surgery, the patient conceived naturally.

Discussion

A previous study indicated that the incidence of adrenocortical oncocytoma is twice as likely on the left side than on the right side, and the incidence of adrenocortical oncocytoma is twice as common in females than in males (2). Adrenocortical oncocytomas are often described as non-functional adrenal tumors and these are discovered via physical examination or assessment of other diseases. Thus, adrenocortical oncocytomas are often misdiagnosed. Adrenal cortical eosinophilic adenoma is mostly non-functional and usually found by physical examination. Common manifestations include feminization of male patients (lack of facial and body hair; chest and buttocks are developed), masculinization of female patients (Breast atrophy, shoulder and hip fat disappearance, menstruation reduction or disappearance; Male characteristics such as beard and pubic hair are male-like, muscular, acne on face and chest, enlarged Adam's apple and deep voice) and Cushing's syndrome, accounting for 17-50% (6). The present study reports the case of a patient with adrenocortical oncocytoma with endocrine abnormality. At present, the pathophysiological mechanisms of adrenocortical oncocytoma are yet to be fully elucidated; however, *in vivo* animal experiments have reported that N-nitromorpholine is an important inducer of eosinophil proliferation (7,8). Following N-nitromorpholine treatment, excessive proliferation of mitochondria is observed as a compensation mechanism, leading to formation of adrenocortical oncocytoma (7,8). Duregon *et al* (9) demonstrated that development of adrenocortical oncocytoma may be due to mutations in the mitochondrial genome, leading to proteins being encoded in eosinophils. In addition, Song *et al* (10) assessed the significance of base mutations in the non-coding control region (D-loop region) of mitochondrial (mt)DNA in oncocytoma, using thyroid and renal oncocytoma and corresponding healthy tissue; D-loop region of mtDNA, particularly hypervariable region I, was a mutation hotspot of oncocytoma, and this mutation may have caused changes in the replication rate of mtDNA, which is associated with the abnormal function of mitochondria.

The presence of adrenocortical oncocytoma may not be revealed using imaging; thus, diagnosis of adrenocortical oncocytoma is complex. Although the observed tumor is often large in size (median diameter, 80 mm), the majority of these tumors possess a complete capsule. Thus, the tumor may continue to grow non-invasively (11-13). In previous studies, imaging of

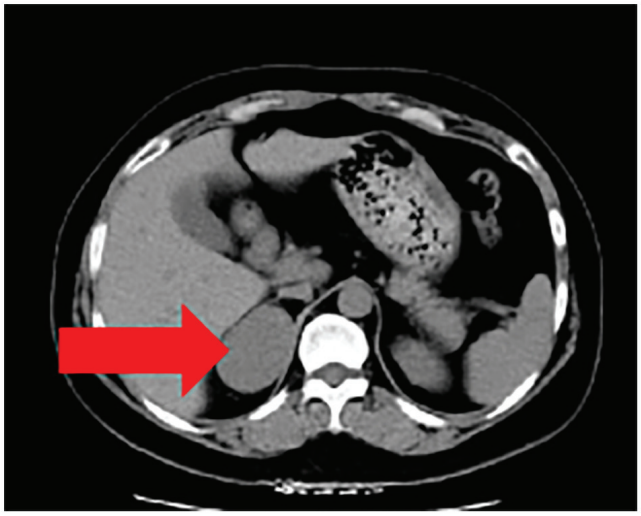

Figure 1. Cross-sectional adrenal CT scan. A cross-section of the adrenal gland revealed a tumor (45x40 mm; arrow) on the right adrenal gland with a CT value of 46 Hounsfield Units and uniform density. The presence of pheochromocytoma or lymphoma was considered. CT, computed tomography.

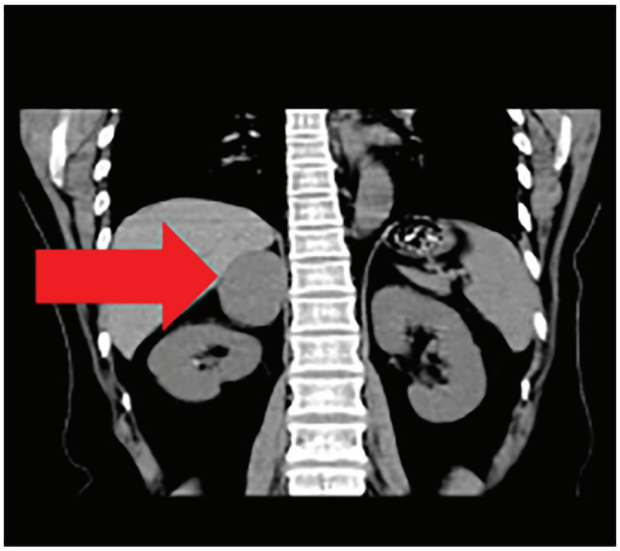

Figure 2. Coronal adrenal CT scan. The coronal CT scan of the adrenal gland revealed a tumor (45x40 mm; arrow) on the right adrenal gland. The presence of pheochromocytoma or lymphoma was considered. CT, computed tomography.

adrenocortical eosinophilia revealed uniform density, with a CT value of 20-40 HU. Furthermore, results of enhanced CT scans revealed an uneven enhancement (11-13). Often, adrenocortical oncocytoma is misdiagnosed as large adrenal pheochromocytoma; however, pheochromocytoma is more hemorrhagic and necrotic than adrenocortical oncocytoma. In addition, the majority of pheochromocytomas are accompanied by internal scars (11). Adrenal cortical oncocytoma also demonstrates low signal intensities on T1 and T2 weighted images, with uneven enhancement and vascular shadows (11). Results of previous studies have reported that adrenal cortical oncocytomas are 20-200 mm in diameter (median diameter is 80 mm), round, possess a complete envelope, are brown or yellowish-brown in color and demonstrate bleeding or necrosis (1,11,12). Furthermore,

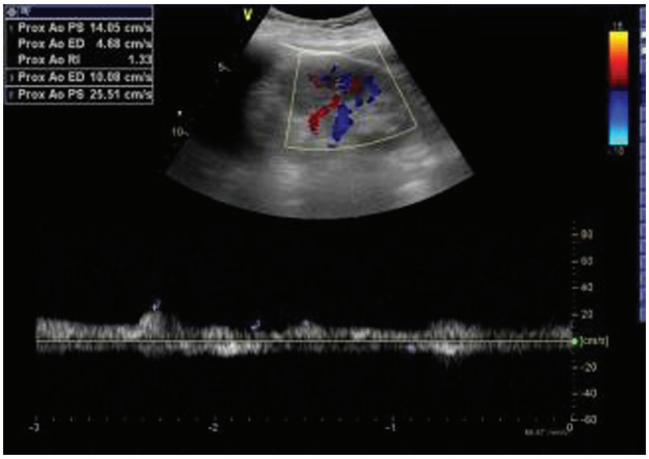

Figure 3. No abnormality in the color Doppler scan of renal blood vessels.

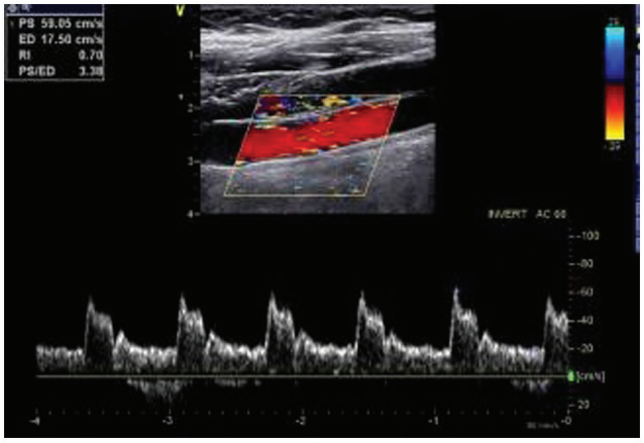

Figure 4. No abnormality in the color Doppler scan of cervical blood vessels.

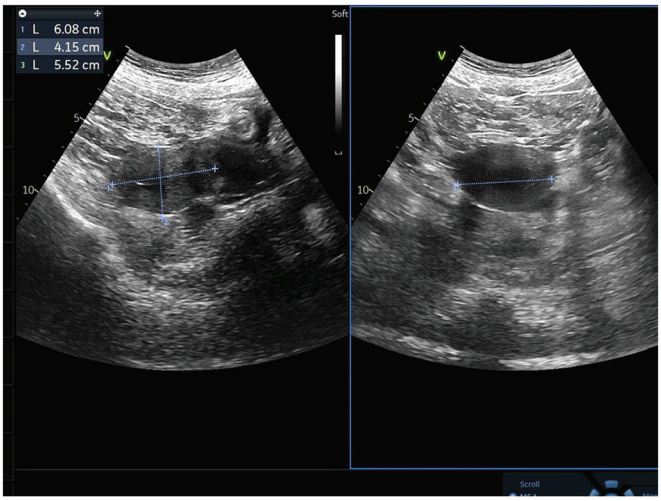

Figure 5. No abnormality by gynecological color Doppler ultrasound scanning.

immunohistochemical analysis has revealed positive α-inhibin and melan-A and negative S100 staining (11,14). However, immunohistochemical markers are limited in differentiating between benign and malignant adrenocortical oncocytoma.

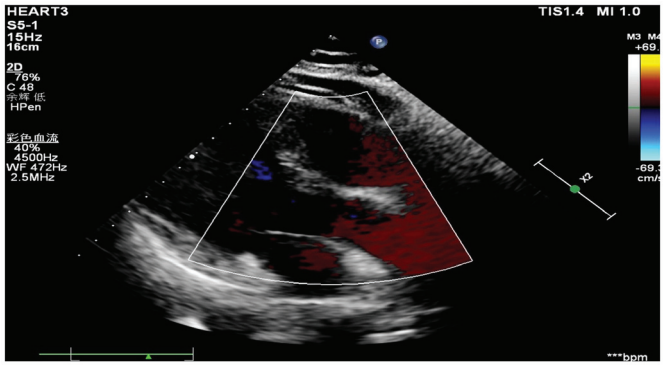

Figure 6. No abnormality in the color Doppler ultrasound scan of the heart.

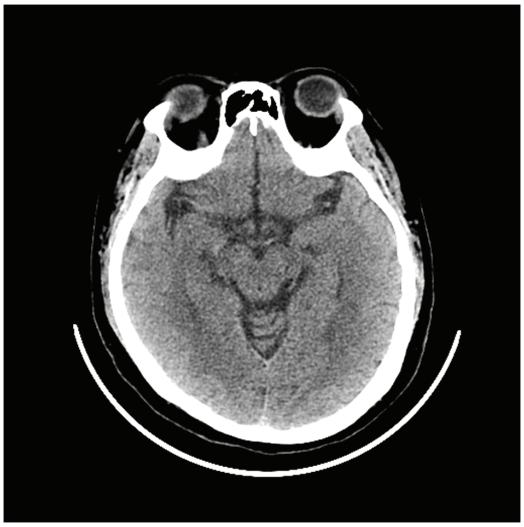

Figure 7. Computed tomography of the skull revealed no abnormality.

Figure 8. Solid specimen of the adrenal tumor excised during surgery. The size of the tumor was 35x60x60 mm^3 and it was dark brown in color, solid and soft.

According to the criteria described by Wong *et al* (15), the following pathological characteristics are indicative of adrenocortical oncocytoma: i) >5/50 high power field atypical mitotic images and ii) venous infiltration. The secondary criteria include the following pathological characteristics: i) Tumor diameter >100 mm and/or mass >200 g; ii) necrosis; iii) capsule infiltration and iv) blood sinus infiltration. Notably, malignant adrenocortical oncocytoma is diagnosed following the presence of any one of the main evaluation criteria; benign adrenocortical oncocytomas do not meet any one of the main or secondary evaluation criteria and adrenocortical oncocytomas meet ≥1 of the secondary evaluation criteria. In the present case, the size of the observed tumor was 35x60x60 mm^3, and necrosis, capsule invasion or blood sinus invasion were not observed. Thus, the secondary criteria were not met. In addition, pre-operative imaging of the head, abdomen and blood vessels did not reveal other tumors. Following the observation of further postoperative pathological manifestations (tumor cells are flaky, while the cytoplasm of tumor cells is eosinophilic and fine granular), benign adrenal cortical eosinophilia was determined.

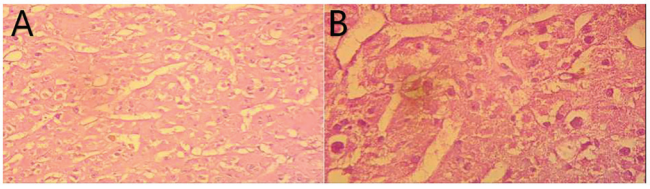

Figure 9. Paraffin-embedded tissue sections revealed that the tumor was mainly composed of eosinophilic epithelial cells, which were diffusely arranged. Only acinar, tubular or beam-like structures were observed in the focal area. Magnification, (A) x100 and (B) x200.

The main treatment of adrenocortical oncocytoma is surgical resection, and the most common surgical methods include minimally invasive laparoscopy or traditional laparotomy (1,7,16,17). A previous study revealed that open surgery is optimal when the diameter of the tumor is >60 mm (16). Following development of minimally invasive techniques, laparoscopic adrenalectomy is considered the gold standard of adrenalectomy and laparoscopic surgical methods have developed transabdominal, retroperitoneal and robot-assisted approaches. However, it remains to be established whether laparoscopic surgery or open surgery is optimal for tumors with a diameter of >60 mm, considering the potential for malignancy prior to surgery (7). In the present case, the size of the adrenocortical oncocytoma was 35x60x60 mm^3, and the right adrenal tumor was resected using an abdominal approach. No complications occurred during or after the operation. Therefore, the present study demonstrated that adrenal surgery was both safe and effective, and a transabdominal approach with improved vision should be used in treatment of patients with a large tumor volume.

In conclusion, Cushing's syndrome caused by an adrenocortical oncocytoma is a rare adrenal tumor disease. The tumor observed in the patient described in the present case was malignant and misdiagnosis occurred. An accurate diagnosis may be achieved following both pathological examination and immunohistochemical analysis. Laparoscopic adrenal tumor resection exhibits numerous advantages, including low levels of associated trauma, reduced recovery time and fewer complications. Thus, the treatment used in the present study was both safe and feasible.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CG and ZG confirm the authenticity of all the raw data. CG and ZG conceived and design of the work, analyzed and interpreted data and wrote the manuscript. QJ, MT, JL and YZ performed imaging and designed the experiments. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of The People's Hospital of Wuchuan (Zunyi, China). The ethical batch number is WCXYYLL-2023-012.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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